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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,285	06/08/2000	Guo-Liang Yu	PF343P3C4	1326

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EXAMINER
PRASAD, SARADA C

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n No. 09/589,285	Applicant(s) YU ET AL.	
	Examiner Sarada C Prasad	Art Unit 1646	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *89-95,98-104,107-110,113-116,119,121,126-130,133,135,140-144,147,149,212-218,221-227,230-233,236-242,245-256,259-267,270-278* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12.
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

Continuation of Disposition of Claims: Claims pending in the application are 89-95,98-104,107-110,113-116,119,121,126-130,133,135,140-144,147,149,212-218,221-227,230-233,236-242,245-256,259-267 and 270-278.

Continuation of Disposition of Claims: Claims rejected are 89-95,98-104,107-110,113-116,119,121,126-130,133,135,140-144,147,149,212-218,221-227,230-233,236-242,245-256,259-267 and 270-278.

Detailed Action

1. Receipt of Applicants' arguments and amendments filed in Paper No. 11 (5/3/02) is acknowledged. Supplemental IDS (Paper No. 12), replacement of sequence listing are also acknowledged. As per applicants' request, claims 1, 17, 19, 26-88, 96-97, 105-106, 111-112, 117-118, 120, 122-125, 131-132, 134,136-139, 145-146, 148, 150-211, 219-220, 228, 229, 234, 235, 243, 244, 257, 258, 268 and 269 have been cancelled, amendments to claims 89, 98, 113, 119, 121, 126, 133, 135, 140, 142, 144, 147, 149, 212, 221, 226, 230, 236, and 250 have been entered, new claims 275-278 have been added, and currently claims 89-95, 98-104,107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, 236-242, 245-256, 259-267, 270-278 are pending and are under consideration for examination.

2. Applicants' arguments filed in Paper No. 11 (5/3/02) have been fully considered but were deemed persuasive in part. The issues remaining are stated below. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. New title is acknowledged.

3b. Substitute specification (Paper No. 10) is entered.

Claim Rejections - 35 USC § 112 first paragraph

Scope of Enablement

4a. Claims 89-95, 275, 276, 98-104, 110, 277-278, 113-117, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 236-242, 245-249, 250-263 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulation of B-lymphocyte proliferation, comprising administering to an individual an

effective amount of a full length protein comprising an amino acid sequence of SEQ ID No. 2, or amino acid sequence comprising residues 134-285 corresponding to extracellular region of neutrokine-α, does not reasonably provide enablement for a method of stimulation of 'B-lymphocyte differentiation or survival', or 'leukocyte proliferation' or 'lymphocyte proliferation' or treating 'any and all immunodeficiencies', comprising administering a therapeutically effective amount of any other 'variants or portions of SEQ ID No. 2' as set forth in Paper No. 8 (11/6/01) and reiterated here as follows.

Applicants' assertion that the region of residues 134-285 of SEQ ID No. 2 represents the extracellular region, and would be equivalent to full length polypeptide in exerting the expected functionality to induce B cell proliferation is found to be persuasive.

Applicants assert that the claimed method merely requires that the polypeptides of the invention can be used for treatment of the immunodeficiencies, and post filing date publications of Khare et al. McKay et al. and Schnieder et al. corroborate the use of neutrokine-α to treat immunodeficiencies (page 12 of response, Paper No. 11, 2nd para, lines 1-). This argument has not been found to be persuasive. There are two points of lack of enablement under consideration addressed as follows: (i) how induction of B lymphocyte proliferation and enhancement of humoral response by neutrokine-α is not sufficient to provide a predictable treatment for all immunodeficiencies in general, because not all immunodeficiencies are due to same defects; (ii) how the scope of the administered polypeptide portions of neutrokine-α for the instant claimed treatment is not commensurate with the guidance provided in the specification.

Complexities of immunodeficiencies: Characterization of 'immunodeficiency' as one single disorder is extremely broad. In fact, antibody-immunodeficiency disorders comprise a

spectrum of diseases characterized by decreased immunoglobulin levels ranging from complete absence of all classes to selective deficiency to a single class or subclass. Instant claims are also directed to treatment of all imunodeficiencies in general and specifically CVID and IgA deficiency. CVID is characterized by a failure in B cell differentiation, and impaired immunoglobulin production, but with variable clinical presentation. A review of CVID (Allegol Immunopathol 2001, abstract) discloses that the cause of the deficient antibody production in this immunodeficiency is not known. Several *in vitro* studies reveal a significant number of alterations that could explain, such as primary B cell alterations, numerical and functional T cell abnormalities, and defects in the interaction between accessory cells. The alteration typical of CVID is the failure of B cells to differentiate from antibody producing cells; T cell abnormalities could be diminished proliferative response to mitogens, antigens, alteration in the level of production of various cytokines, especially IL-2. Additionally, Saxon et al. report how one type of stimulus, for example retinoic acid alone is not sufficient to provide for B cell differentiation in order to achieve normalization of humoral immunity (abstract). Therefore, stimulating B cell proliferation alone would not provide predictable treatment for even CVID, where the defect appears to reside in an activity which neutrokine-α does not appear to affect.

Individuals with IgA deficiency are predisposed to a variety of diseases. The cause of IgA deficiency is not known. It is not clear if it is due to an arrest in the development of B cells, or if there are other associated deficiencies of B cells that produce other sub classes. The presence of normal number of IgA bearing B cells suggests that the disorder is associated with decreased synthesis or release of IgA or impaired differentiation to IgA plasma cells rather than the absence of IgA B cells. In case of a selective IgA deficiency, the patients have compromised

mucosal immune system, and could result in increased incidence of infection, autoantibodies, autoimmune diseases and cancer (Basic and clinical Immunol.1991, pages 329-330). It is true that the instant neutrokine-α could induce B cell proliferation, but this would not provide T cell responsiveness if the particular immunodeficiency is due to T cell defects.

Further, the phrase 'enhancement of host defenses' recited in claims 236-263 is overly broad. Immunologic host defenses can be antibody mediated, T-cell mediated, in addition to those mediated by complement and or phagocytes (page 634, Basic and Clinical Immunology, 1991). The claim language can be interpreted to mean all of the specific immunological as well as non-specific immunological host defenses for which the specification failed to provide guidance or objective evidence that administration of neutrokine-α would predictably enhance.

Potential of neutrokine-α: Post filing date art provided by the applicants has been given full consideration (Khare et al. Do et al. Mackay et al. Schneider et al.). Each of these citations emphasize the B cell costimulatory activity (both T-cell dependent and T-cell independent), yet did not indicate that it is a treatment alternative for all immunodeficiencies. In fact, each of them also point to the risk of inducing autoimmunity or self reactive antibodies during the enhanced immune response. Schneider et al. state that while BAFF can induce signals in both naive B cells, and germinal center-commited B cells in vitro, the question of translating this observation during normal immune response would have to wait further experimentation (page 1754, column 2, entire 2nd para). They also conclude that several obscure zones remain in our understanding of an immune response, little is known about the mechansims governing the differentiation of a B cell into a plasma cell versus a germinal center B cell, or what are the signals deciding the differentiation of a germinal center B cell into a memory cell or a plasma

cell or what is the role of BAFF in these critical decisions (entire last para, page 1754). Therefore, the potential of neutrokine-α to stimulate B-lymphocyte proliferation is not commensurate with the scope of instant claims for treatment of all immunodeficiencies which have defects in aspects of physiology not affected by neutrokine-α.

Additionally, applicants' arguments regarding scope of administered polypeptides focuses mainly on the ability of one of skill in the art to make and screen to determine which ones are operative and which ones are not. However, it is not predictable that polypeptides comprising the amino acid sequence of amino acid residues n-285 of SEQ ID No.2 where n is an integer in the range of 2-190, or residues 1-m of SEQ ID No.2 where m is an integer in the range of 274-284, or residues n-m of SEQ ID No. 2 where n is an integer in the range of 2-190 and m is an integer in the range of 274-284 would be able to treat immunodeficiency, or even stimulate B-lymphocyte proliferation, or differentiation or survival, because the specification fails to provide where along the entire length of SEQ ID No. 2 that changes or truncation could be made, and retain the functionality of stimulating B lymphocytes. While the skill in the art is high, it is not predictable that one of skill would be able to achieve peptide variants with claimed potential, and it would require undue experimentation to screen the numerous polypeptides absent guidance and predictable success. The specification is only enabling for the full-length polypeptide of SEQ ID No.2, and the soluble form comprising the amino acid residues 134-285 for enhancing B cell proliferation.

Furthermore, Claims 89, 98, 126, 140, 212, 221, 230, 236, 250 are directed to 'a method of treating .....wherein the polypeptide of SEQ ID No.2 or the extracellular domain of it or portions/fragments of it modulate lymphocyte proliferation, differentiation, or survival'. The

specification is not enabling for the practice of these claims, because it is only the B lymphocyte proliferation that the instant neutrokine-α predictably stimulates and not proliferation of all leukocytes or lymphocytes. In fact, the term 'Leukocytes' represents three lines of development from primitive elements: myeloid, lymphoid, and monocytic series which include monocytes, B and T lymphocytes, neutrophils, eosinophils, and basophils (Stedman's medical dictionary) and the term 'lymphocytes' refers to both T lymphocytes and B lymphocytes. Therefore, recitation of leukocytes/lymphocytes in the instant claims is extremely broad, and the specification is not enabled for one of skill to obtain stimulation of all of these cells by the instant neutrokine-α or its derived peptides.

Based on the above discussion, it is not predictable that administration of neurokine-α would provide a method of treating any 'immunodeficiency' as recited in instant claims.

Written Description

4b. Claims 89-95, 98-104,107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 236-242, 245-256, 259-267, 270-278 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as set forth in the previous office action of Paper No. 8 (11/6/01) and reiterated here as follows.

The specification discloses that the amino acid sequence of SEQ ID No. 2, and the region 134-285 of SEQ ID No. 2 stimulate B cell proliferation. However, the specification does not describe variants of SEQ ID No. 2 that share the given properties and are effective in stimulation of B-lymphocyte proliferation or disease treatment.

The claims are drawn to use of a genus of polypeptides that comprise fragments of SEQ ID No. 2 or share % identity with SEQ ID No. 2 without provision of critical structural regions necessary to maintain and achieve the activity of B-lymphocyte proliferation. General procedures for making variants are given by conservative substitutions, deletions, but fail to define what regions are critical to function. The single disclosed example of SEQ ID No.2 and the extracellular domain are not a representative of the entire claimed genus. Although the applicants assert that the types of changes in generating the variants are routine in the art and that methods of identifying active variants are provided, the speciation and the claims do not provide any description as to what changes should be made and where to retain the activity, i.e., where the critical structural features reside. The general knowledge and skill in the art do not substitute the omitted description of the members of the genus.

Furthermore, applicants cite support for the newly added, and amended claims with respect to limitations 'treating an immunodeficiency', or 'CVID', or 'IgA', modulates lymphocyte proliferation, differentiation, or survival'(pages 8-9 of Paper No. 11). Applicants' discussion on the support of the new limitations is given full consideration, but was not found to be persuasive, because the description set forth in the specification as support for the new limitations is by way of contemplation and is prophetic, rather than showing that the applicants are in possession of the claimed invention at the time of filing.

Therefore, one of skill in the art would reasonably conclude that the disclosure fails to provide an adequate written description of a representative number of species of fragments of the polypeptide of SEQ ID No. 2 as broadly claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
July 29th , 2002.

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600